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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,124	09/26/2003	Hidetoshi Inoko	WING-003CIP	2646

24353 7590 07/28/2008

BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
07/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/674,124	INOKO ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-17,19 and 20* is/are pending in the application.

4a) Of the above claim(s) *5-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4 and 18 are cancelled.
Claims 5-17, 19 and 20 are pending.
Claims 5-12 are withdrawn.
Claims 13-17, 19 and20 are examined on the merits.

This Office Action is in reply to Applicants' correspondence of 2/20/2008.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **FINAL**.

1. Please note, the text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Remarks: Priority

2. As indicated in the previous Office Action, the priority document (JP 2002-383869) filed December 9, 2002 included a CD-ROM containing the sequence listing for SEQ ID NO: 1-27,088. The sequences are required for claims 13-17, 19 and 20 of the instant application, and as such the effective filing date for the subject matter of those claims is December 9, 2002.

Withdrawn Objections: Specification

3. The objections to the specification for recitation of hyperlinks and/or other form of browser-executable code, and obvious typographical errors, as set forth in the previous

Office Action, are **WITHDRAWN** in light of the amendments to the specification, which are entered.

Withdrawn Claim Rejections - 35 USC § 112 1st ¶ - Description – New Matter

4. The rejection of claims 18 and 20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the recitation of new matter, is **WITHDRAWN** in light of the cancellation of claim 18 and the amendment of claim 20 such that the claim now depends from claim 17..

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement

5. Claims 13-17, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of identifying a DNA sequence fragment comprising a microsatellite in a human genomic region in which a gene associated with a phenotype exists, comprising:
selecting a combination of DNA sequences comprising SEQ ID NOs: 1-27,088, wherein each of the sequences comprises a microsatellite genetic polymorphism marker;
collecting DNA samples from subjects affected with said phenotype and control subjects not affected with said phenotype;
performing PCR on the DNA samples using forward primers consisting of 15-25 nucleotides wherein the forward primers consist of the same nucleotide sequence as the sequence extending in the 3'-direction from the 5'-terminus of each of the DNA sequences in said combination and reverse primers consisting of 15-25 nucleotides wherein the reverse primers consist of the sequence complementary to the sequence extending in the 5'-direction from the 3'-terminus of each of the DNA sequences in said combination to produce DNA sequence fragments, wherein each of said DNA sequence fragments comprises a microsatellite genetic polymorphism marker;
analyzing alleles of the microsatellite genetic polymorphism markers of said DNA sequence fragments; and

statistically comparing allele frequencies observed in the DNA sequence fragments produced from the affected subjects with those observed in the DNA sequence fragments produced from the control subjects to identify microsatellite polymorphism markers found positive whose allele frequencies observed in the DNA sequence fragments produced from the affected subjects are statistically significantly different from the allele frequencies observed in their corresponding DNA sequence fragments produced from the control subjects, wherein the DNA sequence fragments comprising at least one microsatellite polymorphism marker found positive are in a human genomic region in which a gene associated with a phenotype exists.

does not reasonably provide enablement for a gene mapping method comprising performing PCR using "reverse primers consisting of 15-25 nucleotides extending in the 5'-direction form the 3'-terminus of each of the DNA sequences" of SEQ ID NO: 1-27088 (as recited in independent claim 13 and dependent claim 17). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims of the instant invention are drawn to gene mapping methods in which a particular combination of specific DNA sequences each comprising a polymorphic microsatellite (MS) marker is amplified, and the presence of particular variants within the specific sequences is associated with a phenotype to identify a locus linked to the phenotype.

The claims encompass amplification of the 27,088 DNA sequences of SEQ ID NO: 1-27088 using the broadly claimed reverse primers (as recited in independent claim 13, and dependent claim 17). The reverse primers have lengths consisting of 15-25 nucleotides, but the sequence contained in those primers is broadly and

amorphously claimed as 'extending in the 5'-direction from the 3'-terminus' of the polymorphic DNA sequences. The sequence required of any reverse primer is limited only in that it consists of 15-25 nucleotides, where the sequence required of the primer in so far as it extends in the 5'-direction from the 3'-terminus does not serve to limit the structure of the primers.

The claims thus encompass methods wherein an extremely broad and diverse collection of reverse primers are used in a method that requires the specific amplification of each of SEQ ID NO: 1-27,088 as well as the analysis of variable MS content within each of the recited DNA sequences.

Direction provided by the specification and working example

The instant specification asserts that primers of various particular ranges in length may be used for the amplification of DNA segments that contain microsatellite markers (e.g.: p.45 ¶212; p.35 ¶171). The specification further asserts that there are no limitations on a primer 'so long as it can amplify at least a portion of a target gene region' (p.35 ¶171).

The specification does not particularly identify any primers actually used for DNA amplification in the examples provided in the instant application (pages 44-60) by either primer structure (i.e. specific primer sequence) or other identifying characteristics (e.g. primer length and GC content).

The specification provides the sequences of 27,088 polymorphic DNA segments (i.e. SEQ ID NO: 1-27,088) throughout the human genome. The polymorphic DNA segments are diverse in their structure, with various sequences, lengths, and

positioning of the polymorphic content within each sequence. For example, analyzing only SEQ ID NO: 1-20, the segments range in size from 102 nucleotides to 466 nucleotides and include 7 segments under 200 nucleotides in length.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the amplification of any single nucleic acid sequence is high, the unpredictability associated with using primers as broadly claimed in the instant claims to amplify to required polymorphic content from 27,088 different DNA segments is even higher. There is also unpredictability in extrapolating the teachings of the instant specification to any non-human subjects.

Regarding the breadth of the reverse primers, it is relevant to point out that the claims specifically encompass primers consisting of 15-25 nucleotides, though the language of the claims does not serve to require any particular sequence of the 15-25 nucleotide of the primer (i.e.: it is not clear that the language of 'extending in the 5'-direction from the 3'terminus' requires any particular sequence content). However, in a review of only the first 20 segments in the combination comprising SEQ ID NO: 1-27,088, it is noted that several segments are less than 200 nucleotides in length (i.e. SEQ ID NO: 4, 6, 7, 10, 14, 16, and 17 are 123, 102, 162, 142, 160, 163 and 183 nucleotides in length, respectively), and the specification provides no guidance as to where in any DNA segment the polymorphic nucleotide content is present. As such it is highly unpredictable as to how the primers in the full scope of the claims would be successfully used in a gene mapping method. For example, given the 102 nucleotide

DNA segment of SEQ ID NO: 6, one would have to position the reverse primer and the terminus of the fragment to in fact be assured of amplifying nucleotide content in a manner suitable for associating MS alleles with a phenotype.

Further regarding the breadth of the claimed reverse primers, considering the lack significant structural limitations of the primers (for example, see the analysis of the requirements of the reverse primers as detailed earlier in this rejection), and the requirement that the primers amplify specific genomic content as identified by SEQ ID NO: 1-27,088, it is relevant to point out the importance given to primer design in any amplification procedure. For example, Adb-Elsalam (2003) teaches the various parameters which need to be considered when designing primers for PCR, including length, melting temperature, and sequence (p.94). As such, it is unpredictable as to what reverse primer sequences, other than primer sequences consisting of the complements of the sequences of the DNA segments of SEQ ID NO: 1-27,088 would in fact be suitable for the analysis of the polymorphic MS content in each of SEQ ID NO: 1-27,088, as required by the claims.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the invention in the full scope of the claims. Given the breadth of the reverse primers required for the claimed methods, and the fact that the polymorphic content within each DNA segment is not identified in the instant specification, one would be required to analyze a large amount of possible primers for the amplification of any one

of the DNA segments as set forth in SEQ ID NO: 1-27,088 to determine what primers are in fact suitable for the analysis of polymorphic content in each segment.

Conclusion

After consideration of the teachings of the specification and the working examples, considering the breadth of the claims, and the unpredictability in the art, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Response to Remarks

Applicants remarks indicate that the instant rejection has been addressed by the amendments to the claims (Remarks p.9). However it is noted that the enabled scope as indicated by the rejection requires structural limitations of the reverse primers in both length limitations and sequence content. The rejection indicates as enabled "reverse primers consisting of 15-25 nucleotides wherein the reverse primers consist of the sequence complementary to the sequence extending in the 5'-direction from the 3'-terminus of each of the DNA sequences in said combination". However the claims as amended require only "reverse primers consisting of 15-25 nucleotides extending in the 5' direction from the 3'-terminus of each of the DNA sequences". In this case the lack of a requirement for the actual sequence content of the primers, as would be established by the requirement of "wherein the reverse primers consist of the sequence complementary to the sequence", in view of the sequences as set forth in SEQ ID NO: 1-27088, is addressed in the rejection and not addressed by the current amendments to the claims.

Conclusion

6. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634

/Jehanne S Sitton/
Primary Examiner, Art Unit 1634